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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,562	11/14/2001	Avi J. Ashkenazi	P2730P1C18	2836

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EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,562	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-121 and 123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-121 and 123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/04/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Office Action

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/4/2006 has been entered. The claims have not been amended.

Claims 119-121 and 123 are pending and under consideration. The claims are drawn to antibodies that bind PRO1111 protein.

IDS

The information disclosure statement, filed 8/4/2006, has been considered.

Priority Determination

The utility for the claimed protein is active in a chondrocyte redifferentiation assay. Applicants have established that the PCT application contains the chondrocyte redifferentiation. Accordingly, priority remains set at 3/30/00.

Applicants argument that priority is merited to 9/17/1997 has been fully considered but is not deemed persuasive. Applicants are cautioned that a denial of priority is not a *rejection*, contrary to applicants argument. Applicants continue to argue that the gene amplification assay provides basis for utility. It is noted that whereas applicants previously argued that priority was merited to 6/23/1999, that they now argue an earlier date. This argument has been fully considered but is not deemed persuasive for reasons cited below:

At page 4, applicants argue that they are not required to establish a necessary correlation between gene amplification and protein levels, but merely that a preponderance of the totality of evidence is required. The Examiner takes no issue with this premise, and maintains that the preponderance of the totality of the evidence points to lack of predictability, and in fact, in view of the references newly cited by applicants, argues *against* such a correlation existing, as discussed below.

The first Polakis declaration has been fully considered on the record, and does not require further discussion, in and of itself.

Applicants have submitted a second Polakis declaration, filed 8/4/2006, signed 3/29/2006, which is discussed at pages 4-5 of the response.

In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993).

Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949).

The Polakis II declaration has been fully considered to the following effect:

In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. (1) Dr. Polakis declares that 28 of 31genes identified as being detectably over expressed at the mRNA level were found also to have increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PRO1111 (i.e., data regarding amplification of PRO1111 genomic DNA), and does not disclose any information regarding PRO1111 mRNA levels. This was the main issue with the first Polakis declaration, and remains pertinent; there is no demonstration of *any* mRNA level for PRO1111, hence the theoretical correlation of mRNA with protein is not probative. The fact that needs to be established here is

that a ΔCt value of at least 1.0 would be predictive of increased protein expression. Applicants have never addressed this point directly. Furthermore, there is strong opposing evidence showing that *gene amplification is not predictive of increased mRNA levels* in normal and cancerous tissues See, e.g., Pennica et al., discussed in the Examiner's Answer. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data refer to the mRNA's in question only by UNQ numbers; UNQ419, which is PRO1111, is not represented, and declarant provides no information about the sequences that *are* represented; the assertion in the specification is that PRO1111 had a for 2/9 primary lung adenocarcinoma cell lines, 5/11 primary lung squamous cell carcinomas, and 13/17 colon adenocarcinoma. It is not clear whether any or all of these tissues were represented in the data. There is no indication of *how much* the mRNA and protein were overexpressed, as there is no actual description of the experiment that was done, but rather a conclusory statement as to what was measured, and what it means.

For the reasons above, the Polakis II declaration is not sufficient to overcome the rejection of claims 58-62 under 35 U.S.C. §101 and §112, second paragraph.

The Examiner notes that the two Polakis declarations are not consistent:

In the first declaration, Dr. Polakis declares that "we have identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells". In the second, he states that "we have identified approximately 200 gene transcripts that are present in human tumor ***tissue*** at significantly higher levels than in corresponding normal human ***tissue***."

In the first declaration, Dr. Polakis declares that "In approximately 80% of our observations we have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells." In the second, he states that "of the 31 genes identified as being detectably overexpressed in human tumor tissue as compared to normal human tissue <u>at the mRNA level,</u> 28 of them (i.e. greater than 90%) are also detectably overexpressed in human tumor tissue as compared to normal human tissue <u>at the protein level.</u>"

It cannot be determined whether the two declarations are referring to the same data set, or different data sets. Further, there has been no explanation of why the Declarant now refers to tumor *tissue* rather than tumor *cells,* nor what the perceived significance of this change is.

In the Response of 8/4/2006, Applicant has submitted teachings from Alberts, B. (Molecular Biology of the Cell (3rd ed 1994 and 4th ed 2002)) and Lewin, B. (Genes VI 1997) to support the statements of Dr. Polakis (Polakis II declaration; (see above). Applicant also cites numerous references to emphasize that those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression (such as Zhigang et al., Meric et al. Orntoft et al., Wang et al., Munaut et al., etc.). Applicant asserts that changes in mRNA level generally lead to corresponding changes in the level of expressed protein. Applicant also contends that the references and the Polakis declaration establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

Applicant's arguments have been fully considered but are not found to be persuasive. While the Examiner acknowledges the teachings of Alberts and Lewin, which disclose that initiation of transcription is the most common point for a cell to regulate the gene expression, it is not the only means of regulating gene expression. For example, Alberts also teaches that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including translational control mechanisms and mRNA degradation control mechanisms (see Alberts 3rd ed., bottom of pg 453). Meric et al. states the following:

"The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. [M]ost efforts have concentrated on identifying differences in gene expression at the level or mRNA, which can be attributable to either DNA amplification or to differences in transcription."

However, Meric et al. also goes on to state that gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability (see page 971, Introduction). Meric et al. also teaches that there are a number of translation alterations encountered in cancer, including variations in the mRNA sequence as a result of

mutations, alternate splicing and transcription start sites, alternate polyadenylation sites, and alterations in the components of the translation machinery (see pages 973-974). Celis et al. also teach that "[g]enes may be present, they may be mutated, but they are not necessarily transcribed. Some messengers are transcribed but not translated, and the number of mRNA copies does not necessarily reflect the number of functional protein molecules" (pg 6, col 2).

Applicants have submitted a voluminous new information disclosure statement, with 149 reference, purportedly to show that genomic DNA, as measured for PRO1111, is predictive of protein levels. A number of applicants arguments continue to be, and the vast majority of newly cited references are, directed at the predictability of protein levels when *mRNA* levels are amplified. The Examiner maintains that the most significant issue in this case is that the data are drawn to *genomic* data, and *not* mRNA data. While the Examiner concedes that if *mRNA* levels were shown to be significantly higher in a significant proportion of a given tumor type that such would be indicative of utility for the claimed antibodies, she maintains that such is not predictable based upon the data in the specification, which are specifically drawn to amplification of *genomic* DNA.

While the vast majority of newly cited references are drawn to predictability of protein on the basis of mRNA amplification (and for reasons cited above do not merit further discussion), a single reference, that by Godbout, is pertinent to the issue at hand. However, the Examiner finds applicants interpretation of the reference to be erroneous. Far from teaching predictability for expression of PRO1111 on the basis of a minor genomic amplification, the abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state "*It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell* (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer

and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons."

On the contrary, there is no structure/function analysis in the specification regarding the putative protein encoded by the PRO1111 gene. It is not disclosed, and based upon the sequence searches in this case, the Examiner cannot find any reason to suspect, that the protein encoded by the PRO1111 gene would confer any selective advantage on a cell expressing it. It has no known homology to an RNA helicase or any other protein that would be expected to confer a selective advantage to a tumor cell. Further, it cannot be determined from the abstract whether the level of genomic amplification of the DDX1 gene was comparable to that disclosed for PRO1111.

In summary, of applicants 149 references submitted, only a single one, Godbout, is drawn to the predictability of protein levels based upon genomic DNA amplification, and that one supports the Examiners assertion that it is more likely than not that the PRO1111 protein would *not* be expected to be found in increased amounts in the cells tested by applicants, and thus has no utility as a cancer diagnostic.

An additional reference that provides evidence that gene amplification does not predictably or even predominantly lead to increased transcript is Li et al., Oncogene, Vol. 25, pages 2628-2635, 2006. Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "*In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels*, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma.*"

In summary, of applicants 149 references submitted, only a single one, Godbout, is drawn to the predictability of protein levels based upon genomic DNA amplification, and that one supports the Examiners assertion that it is more likely than not that the PRO1111protein would *not* be expected to be found in increased amounts in the cells tested by applicants, and thus has no utility as a cancer diagnostic.

The remainder of applicants arguments have been fully addressed of record.

In closing, the Examiner notes that submission of *data* showing PRO1111 protein or mRNA to be significantly overexpressed in a significant proportion of samples of any of the tested tumor types would be convincing evidence of utility. However, it remains that aneuploidy is one of the hallmarks of tumor formation, and that the specification as filed shows only levels of genomic amplification consistent with such, and that on the basis of such it is *not* predictable that the PRO1111 protein would be overexpressed in the tested cells.It remains that the art considers that that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The instant specification does not provide this additional information, and thus the skilled artisan would need to perform additional experiments. Since the asserted utility for the claimed antibodies is not in currently available form, the asserted utility is not substantial. Applicants arguments to the contrary fail to meet the urged "more likely than not" standard, but rather fall well within the category that significant further experimentation would be required to determine if the claimed polypeptides have the urged utility, experimentation of the type that was found to be impermissible by the court in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct,.1966).

The effective priority date remains set at 3/30/2000.

Rejections Over Prior Art

Priority is set at 3/30/00.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 119-121 remain rejected under 35 U.S.C. 102(a) as being anticipated by Jacobs, WO 99/50405. SEQ ID NO: 2 of the publication is 99.7% identical to SEQ ID NO: 229 of the instant application. Antibodies are disclosed beginning at page 77, and include monoclonal, polyclonal, humanized, chimeric, and single chain antibodies. At page 78 the disclosure states that the antibodies may be used for detection of protein. Accordingly, the claims are anticipated by Jacobs. Applicants argument pertaining to the priority date in the paper filed 8/4/2006 is not persuasive for reasons cited above with respect to priority date determination.

Claims 119-121 and 123 remain rejected under 35 U.S.C. 102(e) as being anticipated by Shimkets, U.S. Patent Number 6,689,866 or US Patent Application Publication US2003/0054514 A1, or US Patent Application Publication US2003/0003532 A1. The US Patent Application Publications are divisionals of the patent, and differ only in the claims. The '514 publication contains claims to nucleic acids, proteins (see claim 11), and antibodies (see claim 13), and the '532 application contains claims to nucleic acids and vectors. The teachings will be discussed with reference to the issued patent. SEQ ID NO: 9 of the patent is 99.7% identical to SEQ ID NO: 228 of the instant application, at bases 1-2183 (bases 159-2341 of the patent), and encodes a protein 99.2% identical to that of SEQ ID NO: 229. SEQ ID NO: 31 is a fragment of SEQ ID NO: 9, is identified as encoding the extracellular domain (see figures 17A and 17B), which is 100% identical to residues 45-495 of SEQ ID NO: 229. Antibodies are disclosed at column 36,

and include monoclonal, polyclonal, humanized, chimeric, and single chain antibodies. Labeled antibodies are disclosed at column 37, lines 44-45. Accordingly, the claims are anticipated by Shimkets. Applicants argument pertaining to the priority date in the paper filed 8/4/2006 is not persuasive for reasons cited above with respect to priority date determination.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 119-120 and 123 remain rejected under 35 U.S.C. 103(a) as being obvious over any one of Loci AI769814, AI435407 , AI470931, or T15752, in view of Sibson et al. for reasons cited in the previous Office Action mailed 7/1/2004, at page 7. Applicants argument pertaining to the priority date in the paper filed 8/4/2006 is not persuasive for reasons cited above with respect to priority date determination. Applicants further argue that the primary references do not teach protein or antibodies, but rather nucleic acids. This argument has been fully considered but is not deemed persuasive because applicants are arguing the references in a piecemeal analysis rather than in the combination in which they were cited. The Sibson

reference provides ample means and motivation to express the proteins encoded by the nucleic acids and make antibodies to those proteins. . One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Claim 121 remains rejected under 35 U.S.C. 103(a) as being obvious over any one of Loci AI769814, AI435407 , AI470931, or T15752, in view of Sibson et al. and further in view of U.S. Patent Number 5,565,332 (Hoogenboom et al.) in the case of claim 121, or in view of U.S. Patent Number 4,946,778 (Ladner et al.) in the case of claim 122 for reasons cited in the previous Office Action mailed 7/1/2004, at pages 7-8. Applicants argument pertaining to the priority date in the paper filed 8/4/2006 is not persuasive for reasons cited above with respect to priority date determination.

Claim 123 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobs, WO 99/50405 for reasons cited in the previous Office Action mailed 7/1/2004, at page 8. Applicants argument pertaining to the priority date in the paper filed 8/4/2006 is not persuasive for reasons cited above with respect to priority date determination.

Advisory Information

No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114.

See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

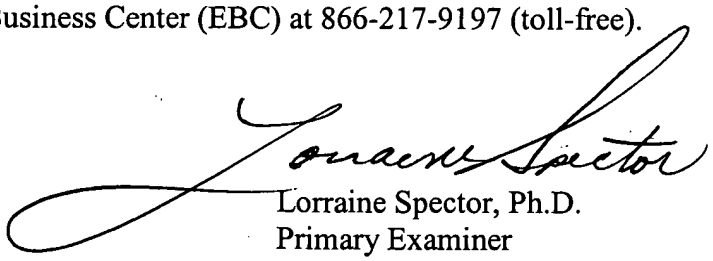
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to 571-273-8300. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Lorraine Spector, Ph.D.
Primary Examiner